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Mixed neuroendocrine-non-neuroendocrine neoplasms of ascending colon: A case report

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ABSTRACT

INTRODUCTION: Neuroendocrine tumor (NET) that develops in the right-sided colon is relatively rare. Coexistence of adenocarcinoma and NET is extremely rare, and such cases are called mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN).

PRESENTATION OF CASE: Colonoscopy in an 85-year-old woman for an anemia examination indicated laterally spreading tumor-nongranular (LST-NG) in the transverse colon. Colonoscopy and endoscopic ultrasonography (EUS) showed that the depth of the tumor invasion was deep submucosal. The tumor localization was diagnosed as transverse colon close to the hepatic curvature by enema. Computed tomography (CT) showed no obvious lymph node or distant metastasis. Based on these findings, laparoscopic transverse colectomy with D2 lymphadenectomy was performed. Pathologically, most of the tumor was well-differentiated tubular adenocarcinoma, but some solid follicles of polygonal tumor cells with poor nuclear atypia were observed. Immunostaining was positive for synaptophysin and diagnosed as NET G1. This tumor consisted of adenocarcinoma and neuroendocrine tumor, so we diagnosed it as MiNEN and classified the tumor as fT1N0M0 fStage I (TNM Classification of Malignant Tumors, 8th Edition). Since it was an early stage cancer, postoperative adjuvant therapy was not performed. No recurrence has yet been noted.

DISCUSSION: Although MiNEN is extremely rare, the detailed pathological specimen observation and diagnosis are important because long-term follow-up after surgery is needed, as is the adequate selection of postoperative adjuvant therapy.

CONCLUSION: It is important to elucidate the mechanisms involved in the coexistence of NET and adenocarcinoma and to apply these findings to future medical care.

1. Introduction

Carcinoid tumors are derived from neuroendocrine cells and are included as neuroendocrine tumors (NETs) in the WHO classification. The number of patients with gastrointestinal NETs has been increasing in recent years. In Japan, the number of new cases per 100,000 population was 2.01 in 2005 and 3.51 in 2010 [1,2]. It is rare to detect NET and adenocarcinoma at the same time and even rarer to detect the coexistence of NET and adenocarcinoma in the same tumor. This work has been reported according to the SCARE criteria [3].

2. Case presentation

An 85-year-old woman had a medical history of hypertension and no surgical history. Laboratory data showed that her complete blood cell count, hepatic and renal functions were within the normal ranges. The serum levels of tumor markers carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) were within normal ranges. Colonoscopy for an anemia examination indicated laterally spreading tumor-nongranular (LST-NG) in the transverse colon (Fig. 1A). The size of the tumor was about 30 mm, and Narrow Band Imaging (NBI) enlargement observation showed that the

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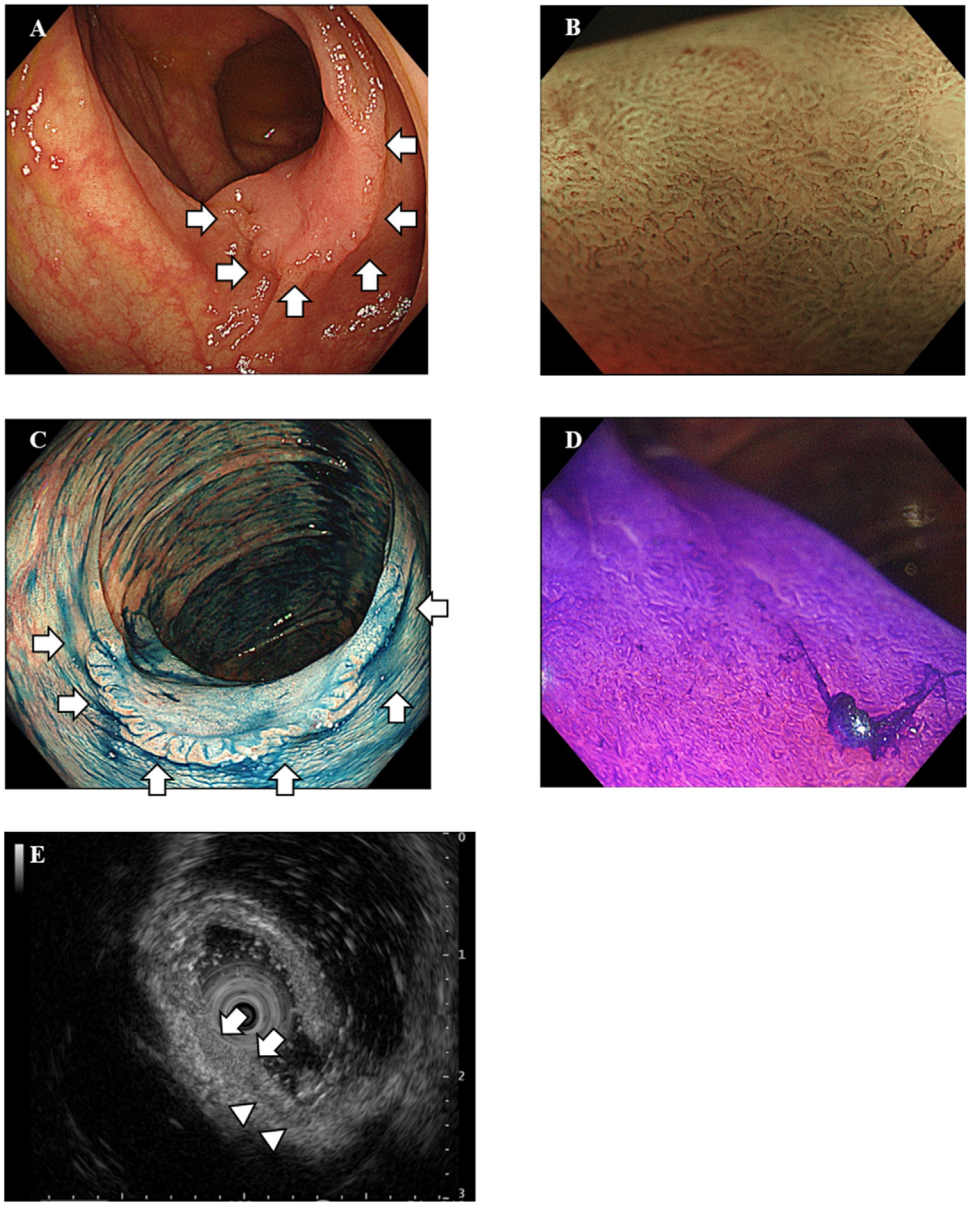

Fig. 1. A: LST-NG existed in the transverse colon. The arrow indicates the outline of the tumor. B: NBI enlargement observation showed that the surface pattern and vessel pattern were not irregular, so the tumor was diagnosed as JNET2B.
C: The pit pattern was IIIL on indigocarmine staining. The arrow indicates the outline of the tumor.
D: The pit structure was irregular on crystal violet staining.
E: EUS depicted the tumor as a low-echoic lesion (arrow) centering on the mucosal layer, and the submucosal layer was preserved. The submucosal layer is partially unclear, suggesting tumor invasion (arrowhead).

surface pattern and vessel pattern were not irregular, so the tumor was diagnosed as JNET2B (Fig. 1B).

Although most of the tumor showed an IIIL pit pattern, as observed by indigocarmine staining, the pit structure was irregular on crystal violet staining, so the tumor was diagnosed as Vi irregular according to the Kudo pit pattern classification (Fig. 1C, D). Endoscopic ultrasonography (EUS) depicted the tumor as a low-echoic lesion centering on the mucosal layer, and the submucosal layer was partially unclear, with tumor invasion suspected (Fig. 1E). Based on these endoscopic findings, the depth of tumor invasion was diagnosed as deep submucosal invasion.

We considered endoscopic resection to be difficult due to the location of the tumor, so surgical resection was necessary. The tumor localization was not clear on computed tomography (CT), but an enema revealed it to be present in the transverse colon near the liver curvature (Fig. 2). CT showed no obvious lymph node metastasis or distant metastasis. Based on the above findings, we classified the transverse colon cancer as cT1N0M0 cStage I (TNM Classification of Malignant Tumors, 8th Edition).

We performed laparoscopic transverse colectomy with D2 lymphadenectomy for surgical resection. No other obvious neoplastic lesions were found in the abdominal cavity. The postoperative course was good, and the patient was discharged on the 12th postoperative day. Pathologically, the tumor was 20 × 20 mm in size, and the muscular layer of the mucosa was ruptured, so the tumor had slightly invaded the submucosa (Fig. 3A, B). No metastasis was found in the resected lymph nodes. This tumor was almost entirely composed of atypical glands that closely resembled tubular adenoma and had Paneth's granular cells. Compared with the common tubular adenoma, the tumor cells showed slightly rounded nuclei with some scattered nucleoli showing a structure that was irregularly branched and coalesced. Therefore, the

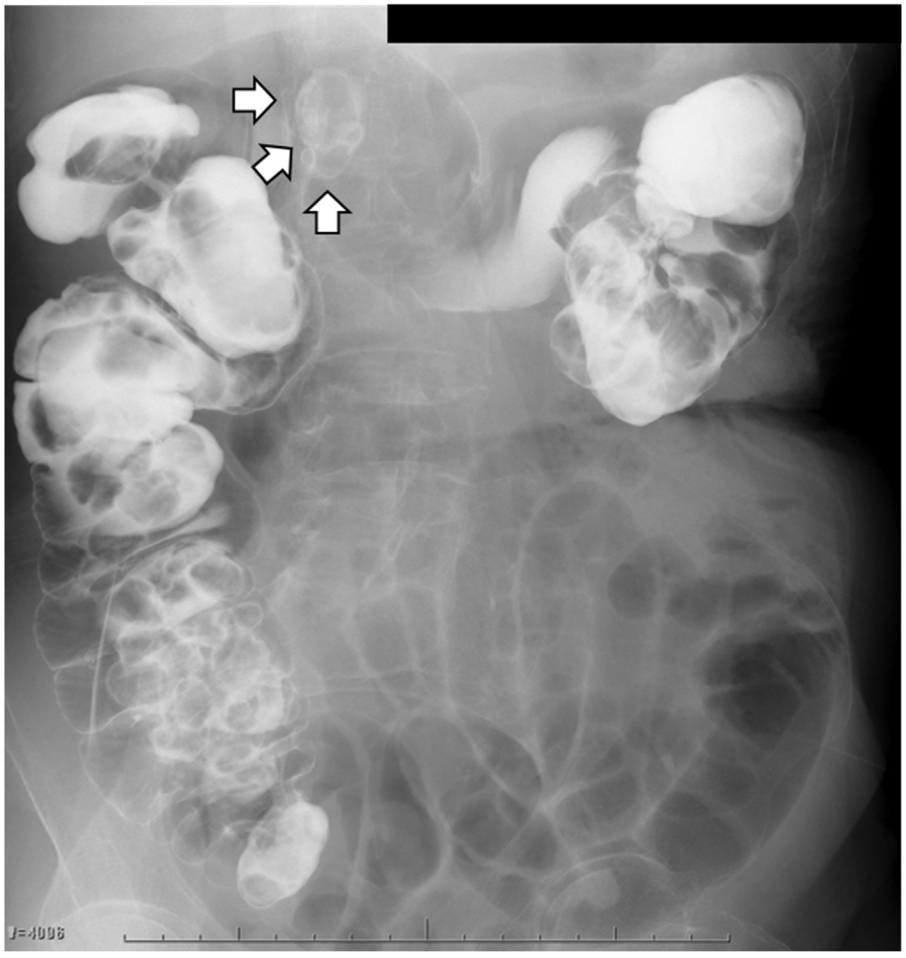

Fig. 2. Enema revealed that the tumor was located in the liver curvature (arrow showed tumor outline).

tumor was considered to be a low-grade highly differentiated-type tubular adenocarcinoma (Fig. 3B). In addition, solid vesicles of polygonal tumor cells with poor nuclear atypia proliferating invasively in the submucosa were observed (Fig. 3B). These cells were positive for synaptophysin and CD56 and negative for Ki-67 and were thus considered carcinoid tumors (NET G1) (Fig. 3C–E).

Based on these pathological findings, the tumor was diagnosed as MiNEN and classified as fT1N0M0 fStage I (TNM Classification of Malignant Tumors, 8th Edition). Since it was an early-stage cancer and the patient was quite old, postoperative adjuvant therapy was not performed. No recurrence has developed.

3. Discussion

We herein report a case of MiNEN in which ascending colon cancer and NET G1 occurred simultaneously in an 85-year-old woman. Colorectal cancer is a common cancer, and adenocarcinoma accounts for 95% of all colorectal cancers. The remaining 5% are mucinous and squamous cell carcinomas. About 1% of colorectal cancer cases are NETs formed in neuroendocrine cells involved in hormonal regulation. These NETs can develop in the pancreas, lungs or gastrointestinal tract.

The revision of the WHO classification in 2000 and 2010 created a histopathological classification based on the grade classification using indices reflecting the degree of differentiation and tumor cell growth dynamics, like the number of nuclear divisions and Ki-67 labeling index. The latest revision of the WHO classification proposed that NEN be classified as either NET highly differentiated type or NEC poorly differentiated type.

Mixed neuroendocrine-non-neuroendocrine neoplasm (MANEC) in the WHO2010 classification was a name mainly applied in cases with the combination of adenocarcinoma and NEC in both components. However, the combination of squamous cell carcinoma or acinar cell carcinoma and high-grade NEC or cases with a NET component may correspond to G1/2. Tumors that correspond to MiNEN are histologically classified into two broad types. One is a combined/biphasic type. This type is composed of neuroendocrine and non-neuroendocrine components such as adenocarcinoma and squamous cell carcinoma. Neuroendocrine and non-neuroendocrine cells proliferate while maintaining locality and thus form a single tumor. The other type is the intermining/amphicrine type. This type is composed of neuroendocrine cells, non-neuroendocrine cells, and amphicrine cells which have either neuroendocrine or non-neuroendocrine cell differentiation. These cells proliferate in close proximity to each other and mix to form a single tumor. In each case, each component accounts for ≥30%, and both components have been both histologically and immunohistologically proven [4–10].

MiNEN is a rare tumor, and its prognosis is unclear due to the heterogeneity of its components, with no well-defined treatment strategy having been established. Generally, the prognosis of MiNEN is said to be intermediate between the prognosis of each component [9,10]. La Rosa et al. classified MiNEN into three grades (high, intermediate and low) according to the prognosis and found that the grade was useful for determining treatment strategies [11] High-grade MiNEN are the most frequent cases, combining

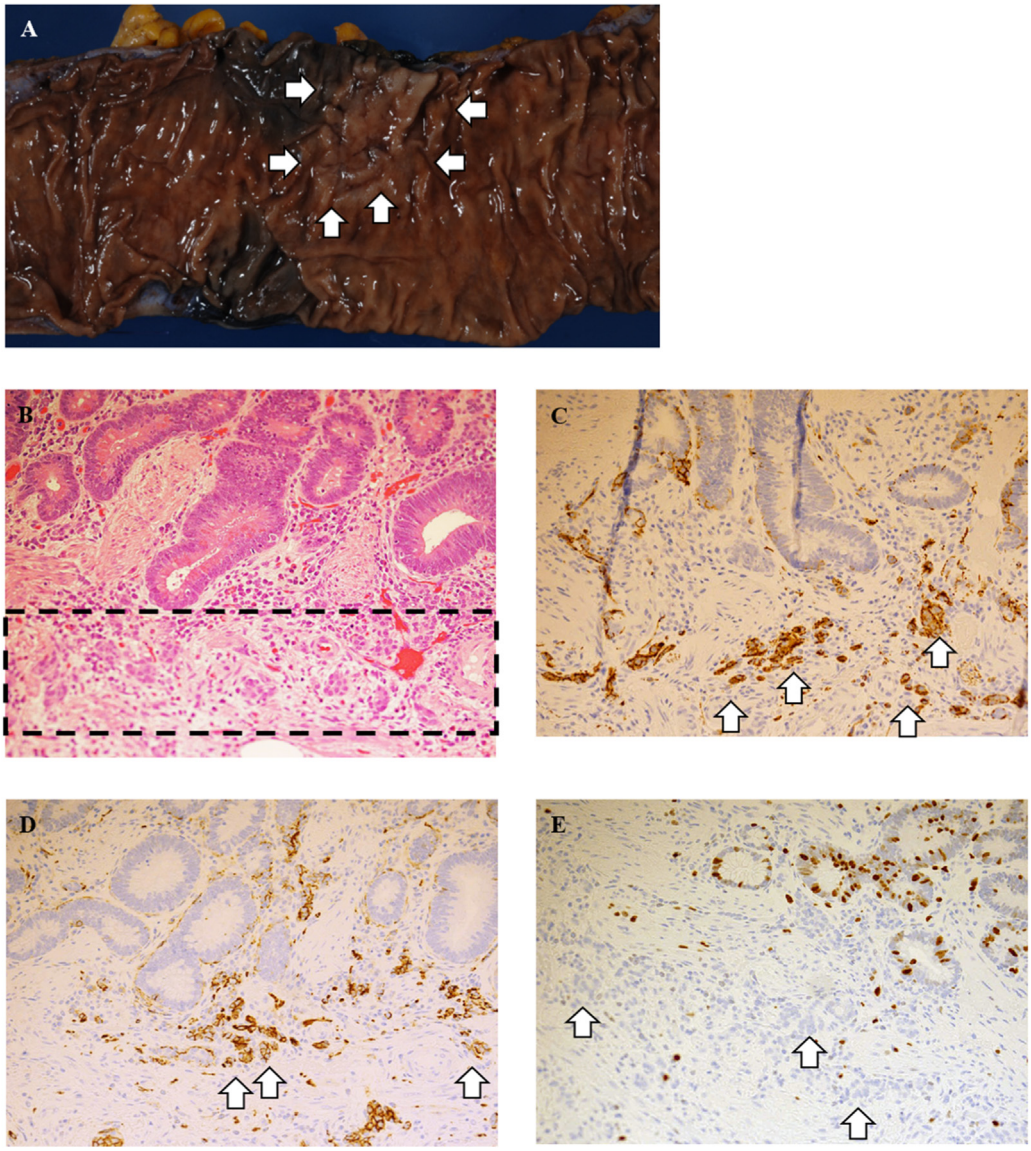

Fig. 3. A: The tumor was 20 × 20 mm in size. The arrow indicates the outline of the tumor.
B: The tumor was mainly a well-differentiated adenocarcinoma, but vesicles in which polygonal tumor cells with poor nuclear atypia had proliferated solidly were observed mainly in the submucosal layer (area enclosed by a broken line).
C: The tumor cells were positive for synaptophysin. The arrow indicates synaptophysin-positive tumor cells.
D: Tumor cells were positive for CD56. The arrow indicates CD56-positive tumor cells.
E: Tumor cells were negative for Ki-67. The arrow indicates Ki-67-negative tumor cells.

NEC with adenocarcinoma or adenoma, with NEC generally considered the most aggressive component [9,12–18]. If the lesion is localized without distant metastases, it can be removed surgically with perioperative chemotherapy. Systemic chemotherapy is recommended in situations involving distant metastases, and etoposide should be combined with cisplatin or carboplatin in the first line, according to the NEC management strategy. Intermediate-grade MiNEN is a combination of well-differentiated NET and non-neuroendocrine cancer. The prognosis generally depends on the non-neuroendocrine carcinoma, but neuroendocrine components must be considered as prognostic factors, especially when G3 NET components are involved [9]. If resectable, surgery should be performed for treatment purposes, and if metastasis is involved, the components identified in the metastases should be targeted for chemotherapy or drugs that are active against both components. Low-grade MiNEN is a combination of well-differentiated NET and adenoma. Low-grade MiNEN is rare and has been reported primarily in the gastrointestinal tract [9]. NETs can metastasize and must be treated as pure NETs.

There are various theories concerning the development of MiNEN, but no clear consensus has been reached. It is said that the simultaneous development of gastrointestinal NET and adenocarcinoma involves an impaired gene expression in stem cells. Kato et al. suggested that CK20 might play a role in the synchronous development of NET and colorectal cancer [19,20].

In the present case, the adenocarcinoma segment developed around the mucosa and partially invaded the submucosa, while the NET component developed around the submucosa and separated from the adenocarcinoma component. In addition, NET components accounted for more than 30% of the entire tumor tissue, so this case was diagnosed as a combined/biphasic type of MiNEN. The present tumor was histologically composed of NET G1 and adenocarcinoma and classified as low-grade according to the classification of La Rosa et al. Adjuvant therapy was not considered

necessary because curative resection had already been obtained and the patient was elderly, but the progress should be followed carefully.

4. Conclusion

In conclusion, we encountered a rare case of ascending colonic MiNEN. Although our case was a low-grade lesion and the prognosis not expected to be bad, it might be necessary to analyze the gene mutation or impaired expression in MiNEN development. It is important to elucidate the mechanisms involved in the coexistence of NET and adenocarcinoma and to apply these findings to future medical care.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

A case report is exempt from ethical approval in our institution.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

Author contribution

Dr. Shoichiro Mukai drafted the article. Yuzo Hirata and Toshikatsu Fukuda had revised the manuscript critically. Sho Ishikawa was an assistant of operation. Toshihiro Nishida revised the histopathological findings. Hiroyuki Egi and Hideki Ohdan were supervision of this manuscript. All authors contributed to study concept or design at this submission and approved the final version.

Registration of research studies

N/A.

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